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The role of ascorbate in brain: therapeutic implications

For many years it was widely believed that the only function of ascorbate in the body was to promote collagen synthesis and that its only role in therapeutics was to treat scurvy. However, research in the last few years has revealed new and important functions for ascorbate in the body, in particular in the brain. Smythies and Tolbert[1] suggested that some 'vitamins' might have some effects not connected with the avoidance of their specific deficiency diseases. These effects might be directed towards brain neurotransmitter systems, in particular dopamine in the case of ascorbate. In 1983 Hoffer[2] proposed that ascorbate might be useful as a protection against autooxidation damage in critical brain areas. Recent evidence shows that these hypotheses are very likely to be correct.

The brain contains the highest level of ascorbate in the body and there are active uptake mechanisms in the choroid plexus and cell membrane to maintain intracellular levels at 16–25 times higher than blood levels. Levels of extracellular brain ascorbate vary greatly according to the activity of the animal, being lowest during sleep and highest with prolonged activity and stress. Some of the mechanisms of its role in the brain have been worked out (see the comprehensive review by Rebec and Pierce[3]). The transport proteins that take up glutamate do so in exchange for ascorbate. Thus uptake of glutamate is accompanied by release of ascorbate. Ascorbate modulates activity at glutamate receptors and also protects glutamate related NMDA receptors against glutamate toxicity. Ascorbate acts directly as a competitive antagonist[4] at dopamine receptors. Numerous biochemical and behavioural tests have shown that ascorbate antagonizes the effects of amphetamine and enhances the effects of the antipsychotic drug haloperidol. Extracellular release of ascorbate in the neostriatum is controlled by the glutamatergic loop that runs from the substantia nigra via the corticoneostriatal pathway[5].

Clinical reports as to whether ascorbate is of benefit in schizophrenia are conflicting. The proposed neuroleptic properties of ascorbate suggests that it should be evaluated only in neuroleptic responsive type 1 cases with positive symptomatology where positive results have been obtained[6]. In autistic patients it attenuates the motor symptoms without much effect on the affective ones[7], which fits in with its postulated mode of action on dopamine systems.

Another clinical area where brain ascorbate is relevant is Parkinson's disease. This may be caused in part by auto-oxidative destruction of the dopamine containing cells in the brain by toxic quinone derivatives of dopamine and by toxic free radical forms of oxygen. Ascorbate and tocopherol (vitamin E) provide the body's main defences against this form of autotoxicity. *In vitro* L-DOPA (dihydroxyphenylalanine) is toxic to DA cells and this is prevented by ascorbate[8]. Ascorbate therapy in early Parkinson's disease delays the need to give L-DOPA by 2 years[9]. The antioxidant deprenyl has given a similar result. Thus, there is a clear case for further studies of the therapeutic role of ascorbate in schizophrenia, autism and Parkinson's disease. Ethanol also causes oxidative stress in the brain and raises the level of dopamine metabolites and lowers brain ascorbate[10].

Conditions such as stroke, hypoxia, ischaemia, seizure activity and trauma all lead to massive release of glutamate in the brain and to a six to eight-fold increase in extracellular brain ascorbate which may represent a defence mechanism especially during reperfusion[11–13].

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